Intracranial hypertension after traumatic brain injury

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Abstract

Traumatic brain injury is a devastating problem with both high mortality and high subsequent morbidity. Injury to the brain occurs both at the time of the initial trauma (the primary injury) and subsequently due to ongoing cerebral ischaemia (the secondary injury). Hypotension and hypoxaemia are well recognized causes of this secondary injury. In the intensive care unit raised intracranial pressure (intracranial hypertension) is seen frequently after a severe diffuse brain injury and leads to cerebral ischaemia by compromising cerebral perfusion. This paper reviews the pathophysiology of intracranial hypertension and summarises current and experimental approaches to its management in the intensive care unit.

Key Words: Brain injury, cerebral perfusion, decompressive craniectomy, head injury, intracranial pressure.

Introduction

Traumatic brain injury (TBI) is a common and devastating problem with a high mortality and a high residual morbidity in survivors. The most cost effective measures of course are all preventative, including public health education, the mandatory use of seatbelts in cars and helmets on motorcycles, appropriate speed limits and improved road design. When an injury has occurred, however, it then becomes crucial for the prehospital and hospital management to be focused on preventing secondary injury and minimizing the chances of a poor outcome. In the neurointensive care unit the issue above all else is to maintain cerebral perfusion and prevent cerebral ischaemia. Intracranial hypertension leads to cerebral ischaemia and is often the most difficult management problem after a head injury. It is disappointing that while intracranial hypertension was identified as the prime pathophysiological entity in TBI in 1951, there are still few therapeutic options available to the clinician and the overall quality of research is poor.

Epidemiology

Traumatic brain injury is the commonest cause of death in young males in developed countries and has been termed a ‘silent global epidemic’. Approximately half of all trauma deaths include a significant TBI which contributes to the death. It is estimated that every year 600,000 people suffer a TBI in the United States of America (0.3% of the population per year). 42% of these are hospitalized and the costs, both in hospital and subsequently, can be massive.

The Australian Traumatic Brain Injury Survey (ATBIS) prospectively followed all patients who had been admitted to the intensive care unit of 16 tertiary referral trauma centers over six months in 2000 (Myburgh J, personal communication). Of 635 patients the hospital mortality was 20.6%, with 6 month mortality 24% and 12 month mortality 27%. Survivors were evaluated at 6 and 12 months with the Glasgow Outcome Score (GOS). At 6 and 12 months, 45% and 41% of survivors respectively had an ‘unfavourable’ dichotomized GOS (severely disabled or vegetative). Thus a good outcome is achieved in only about 40% of TBI patients admitted to intensive care.

Unfortunately good India data are not available and collection of these data should be a priority to inform
appropriate head injury management in that country.

**Pathophysiology**

The ‘primary injury’ is sustained at the time of impact, with high energy acceleration or deceleration of the brain within the rigid cranium. The ‘secondary injury’ is a complex process driven predominantly by cerebral ischaemia and mediated by changes in cerebral blood flow, local and systemic inflammation, metabolic derangements, necrosis and apoptotic death of neurons. While nothing can be done about the primary injury for an individual, the focus of modern neurointensive care is to aggressively prevent or minimize any secondary injury, predominantly by minimising cerebral ischaemia. Analysis of the US Traumatic Coma Data Bank (TCDB)\(^5\) identified hypotension (systolic blood pressure < 90 mmHg), hypoxia (SpO\(_2\) < 90% or PaO\(_2\) < 50 mmHg), hypoglycaemia, pyperpyrexia (temp > 39\(^\circ\) C) and prolonged hypocapnia (PaCO\(_2\) < 30 mmHg) as independent predictors of a poor outcome after head trauma. A more recent study again found hypoxia, hypotension, hyperthermia and intracranial hypertension\(^6\) the strongest predictors of poor outcome after TBI.

The ‘Monroe - Kelly Doctrine’\(^7,8\) states that incompressible structures within the cranial vault are in a state of volume equilibrium, such that any increase of the volumes of one component (i.e. blood, CSF, or brain tissue) must be compensated by a decrease in the volume of another. If this cannot be achieved then pressure will rise and once the ‘elastance reserve’ of the intracranial space is exhausted then small changes in volume can lead to precipitous increases in pressure.

More complex is the variation of cerebral blood flow over time. Three distinct patterns of blood flow have been recognized after TBI. Sequentially these are the phases of hypoperfusion, hyperaemia and vasospasm.\(^9\) Therapies directed towards hypoperfusion on day one may be quite inappropriate during the hyperaemic phase on day four!

During the hypoperfusion phase cerebral blood flow is reduced with resultant global and regional ischaemia. Cerebral autoregulation is impaired and cerebral blood flow depends directly on systemic blood pressure. Neuronal ischaemia during this phase leads to so called ‘cytotoxic’ cerebral oedema and intracranial hypertension. The hyperaemic phase may follow from about day 4, in about 30% of patients, and may persist for a week or more. Autoregulation begins to recover and the combination of hyperaemia, inflammation and blood brain barrier injury leads to so called ‘vasogenic’ cerebral oedema. Lower cerebral perfusion pressures may be acceptable as attempts to maintain high cerebral perfusion can actually lead to worsening intracranial hypertension.

A small cohort of patients, particular those with significant traumatic subarachnoid haemorrhage, may subsequently have a period of cerebral vasospasm, which is often complicated by cerebral hypoperfusion and even infarction.

**Principles of management**

Formal evidence based guidelines for the management of TBI were published by the Brain Trauma Foundation in 2000\(^10\) and revised in 2003,\(^11\) and complement similar guidelines elsewhere such as the European Brain Injury Consortium.\(^12\) Whilst these guidelines illustrate how little good quality evidence exists, they provide a framework upon which TBI research can develop, and all modern TBI management should be consistent with the principles in these guidelines. The adoption of standardised treatment protocols has been clearly shown to improve outcomes in ‘before and after’ studies in different ICUs.\(^13\)

**Basic treatment of traumatic brain injury**

Initial resuscitation is according to the principles of Advanced Trauma Life Support (ATLS)\(^14\) with due attention to Airway, Breathing, Circulation, Disability and Exposure - the single most important thing in a head injury is a clear and unobstructed airway! An early, unsedated Glasgow Coma Score (GCS) is helpful in defining severity of TBI and to some extent for prognosis. Comatose patients should be intubated - the basic principle is that “GCS 8 means intubate” and this should be achieved by rapid sequence induction as soon as there are appropriately skilled personnel available. The cervical spine must be protected, and is assumed to be injured until definitively cleared.

Intubated patients should be ventilated to normocarbia, maintaining P\(_a\)CO\(_2\) between 36 and 40 mmHg. This is best assessed by end tidal capnography, and generally corresponds to P\(_{E}\)CO\(_2\) 31 - 35 mmHg. All ventilated head injury patients should have continuous capnography.
They must be kept well oxygenated with PaO\textsubscript{2} > 90 mmHg and SpO\textsubscript{2} > 95%. Hypoxaemia dramatically worsened outcomes in the TCDB dataset. Ventilation can become difficult if there are other major injuries particularly chest injuries, aspiration of gastric contents, or if the acute respiratory distress syndrome develops. Appropriate positive end expiratory pressure (PEEP) should be used. There is no evidence that PEEP impairs cerebral blood flow or elevates ICP\textsuperscript{15} and indeed ICP may improve with improved oxygenation.\textsuperscript{16}

An early non contrast CT brain is required to guide subsequent therapy. All patients should have arterial and central venous lines, as soon as practical. They should be fluid resuscitated to euvoalaemia and if necessary vasopressors used to maintain blood pressure - again a single episode of hypotension dramatically worsened outcomes in the TCDB.\textsuperscript{17}

ICP monitoring is used in all severe head injuries unless there is a severe coagulopathy. Once an ICP monitor has been placed fluid and vasopressors are used to maintain a Cerebral Perfusion Pressure (MAP - ICP) of 60 mmHg. Any patient with elevated ICP needs to be adequately sedated, and many agents are suitable for this purpose.

Patients should be nursed 30° head up unless haemodynamically unstable or needing large doses of noradrenaline, or prevented by unstable spinal or pelvic injuries. This both maximises venous drainage (preventing a increase in the venous cerebral blood volume) and minimises ventilator associated pneumonia. Indeed in one trial the 30° semirecumbent position both significantly reduced ICP and significantly improved CPP without any adverse effect on cerebral oxygenation.\textsuperscript{18}

For ongoing fluid management an isotonic crystalloid is used to maintain serum sodium 140 - 149 mmol/l and clinical euvoalaemia. Patients should be kept normothermic (37°C) with appropriate use of forced air warming or cooling, and paracetamol. Stress ulcer prophylaxis is provided with an H\textsubscript{2} antagonist. Phenytoin decreases the risk of early posttraumatic seizures,\textsuperscript{19} but there is no benefit continuing the drug past 7 days. Enteral nutrition is commenced within 24 hours of injury - gastroparesis is common after TBI and a postpyloric tube may be necessary. Normoglycaemia is maintained with an insulin infusion if necessary, as there is an association between hyperglycaemia on admission and poor neurological outcomes.\textsuperscript{20} Sequential calf compressors are used routinely for deep venous thrombosis prophylaxis, and subcutaneous heparin added after 48 hours if there is no evidence of ongoing bleeding.

**Cerebral perfusion pressure**

Maintenance of cerebral perfusion is the primary goal in most guidelines, to minimize any secondary insult caused by hypoperfusion. The cerebral perfusion pressure (CPP) is defined as the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP). An ICP monitor of some kind therefore needs to be inserted early in all patients with severe traumatic brain injuries (presenting GCS < 8) and abnormal CT scan (haematoma, contusions, oedema or basal cistern compression), as well as those with a normal CT and any of age > 40 years, motor posturing and systolic blood pressure < 90 mmHg. Ventriculostomy is preferred, as this allows the therapeutic option of CSF drainage. A parenchymal catheter (Camino or Codman) is used if ventriculostomy is not feasible. Fluid filled subdural catheters were popular in the past but are extremely inaccu rate and are no longer recommended.

Arbitrarily a CPP of 60 mmHg is targeted in adults (having been revised from 70 mmHg in the 2003 guidelines). There is no evidence of benefit in maintaining a higher CPP and significant adverse systemic effects when high doses of catecholamines are required to maintain a higher CPP. A retrospective analysis of the database of a negative drug trial\textsuperscript{21} could not detect benefit of a CPP above 60 mmHg and described a much higher incidence of the acute respiratory distress syndrome with aggressive attempts to maintain a higher CPP. Some centres attempt to individually determine the optimal CPP for each patient, assessing adequacy of cerebral blood flow with jugular bulb oximetry, transcranial Doppler, near infrared spectroscopy or more recently brain tissue oximetry, and using Xenon enhanced CT to discriminate between diffuse and local ischaemia.\textsuperscript{22}

One specific strategy (the 'Lund therapy') uses measurement of cerebral blood flow to demonstrate adequate cerebral perfusion, while reducing CPP to > 50 mmHg using $\beta$-blockade, clonidine and dihydroergotamine.\textsuperscript{23} This 'cerebral blood volume regulation' approach requires
further evaluation and validation outside of the University of Lund.

**Specific treatment for intracranial hypertension**

A spontaneous and persisting ICP above 20 mmHg is generally accepted as requiring treatment. If the ICP is elevated despite basic intensive care measures, first recheck everything! The patient should be optimally positioned with head elevated and without any external pressure on the neck. Optimal ventilation must be confirmed and further sedation administered to exclude undersedation. An urgent repeat CT scan is required to exclude an operable mass lesion.

If a ventriculostomy is in place, CSF can be drained. If the patient is on a critical point of the intracranial elastance curve then drainage of 3 - 5 ml CSF can have a dramatic effect on ICP. Often these patients require continuous drainage of CSF.

**Hyperventilation**

Hyperventilation became popular in the 1970s as a means to reduce ICP in severe TBI. It subsequently became clear however that patients who were prophylactically hyperventilated had worse outcomes. This is because of the cerebral ischaemia caused by the hyperventilation induced vasoconstriction. Hyperventilation should only ever be used as a ‘desperation’ measure to buy some time on the way to an operating room.

**Fluid management**

In the past patients were ‘kept dry’ but this is inconsistent with the goal of maintaining cerebral perfusion. Cerebral oedema can occur no matter what fluid has been administered. Euvolaemia should be the primary resuscitative goal for patients with TBI. Choice of fluid is extremely controversial and mainly comes down to the individual biases of clinicians. The Saline versus Albumin Fluid Evaluation (SAFE) trial however showed improved outcomes in the trauma cohort (17% of 6997 patients) if 0.9% saline rather than 4% albumin was used for fluid resuscitation. It appears that the survival difference is seen mainly in the subgroup who sustained a head injury (defined as GCS < 14 with an abnormal CT scan on presentation). However this study used overall 28 day mortality as its primary endpoint and this is not a meaningful outcome in TBI. The SAFE investigators are currently conducting a 2 year followup of all the TBI patients using the extended Glasgow outcome score (GOSE) for functional evaluation at this time.

**Osmotherapy**

20% mannitol is the traditional osmotic agent used in TBI but has significant disadvantages and recently hypertonic saline has been promoted as the agent of choice. Mannitol decreases interstitial cerebral oedema and thus intracranial pressure. This mechanism probably only works in the presence of an intact blood brain barrier, however, and over a narrow range of plasma osmolality (290 - 330 mosm/kg). In addition mannitol acts as an osmotic diuretic and can precipitate hypovolaemia, which impairs cerebral perfusion and can worsen underlying cerebral ischaemia. If the blood brain barrier is disrupted mannitol will enter the brain and actually increase the cerebral oedema.

Hypertonic saline (HS) has a similar osmotic effect on the cerebral interstitium but acts as a plasma volume expander and does not induce an osmolar gap as mannitol does. There is evidence that hypertonic saline also has neurohumoral and vasoregulatory effects, and may act as a cerebral vasodilator in the presence of vasospasm. A recent trial directly compared hypertonic saline and mannitol. 20 consecutive patients with resistant intracranial hypertension received boluses of either HS or mannitol to an endpoint of clinical resolution. There were significantly fewer episodes of ICH in the HS group (P < 0.01) with lower rates of clinical failure (P < 0.01). Patient selection however is important and a recent Australian trial examining the routine prehospital use of HS in patients with severe TBI showed no difference in outcomes at 6 months.

**Hypothermia**

Mild hypothermia has been advocated as a therapy for TBI but remains controversial. It is clearly beneficial in animal models but human trials have been complicated by the effects of hypothermia on coagulation, infection and myocardial performance. Despite being effective in decreasing ICP, induced hypothermia was not effective in a recent large multicentre trial, the National Brain Injury Study: Hypothermia. Retrospective analysis suggested that patients who were hypothermic on arrival in hospital did better if they were not warmed aggressively. There is probably a place for mild therapeutic hypother-
mia in selected patients but more clinical research is required to identify the appropriate subgroups.

**Neuromuscular blockade**

Neuromuscular blockers (NMB) are commonly used to abolish the ICP surges caused by suctioning or coughing. There is some retrospective evidence however that raised ICP and worse outcomes are more likely if NMBs are used and it seems reasonable to restrict use to patients with a propensity to ICP surges.

**Barbiturates**

Barbiturate coma is effective in reducing ICP. There are many complications however, particularly immunosuppression and infectious complications as well as the predictable hypotension. There is no clinical evidence of improved patient outcomes after barbiturate coma though an infusion of thiopentone to achieve EEG burst suppression is still commonly used when trying to control severe refractory intracranial hypertension.

**Experimental therapies**

**Corticosteroids**

High dose steroids had been used in head injury in the 1970s and then abandoned because of the complications seen. The question has been revisited after the Cochrane collaboration published a systematic review suggesting possible improved outcomes. The large Corticosteroid Administration after Severe Head Injury (CRASH) trial in the United Kingdom has recruited over 4000 patients so far and will hopefully provide a definite answer to this question. A more recent metaanalysis of 19 trials and over 2000 patients suggests an insignificant difference in mortality only and steroids currently cannot be recommended.

**Decompressive craniectomy**

The concept of surgical decompressive craniectomy has attracted a lot of interest in the last decade. It intuitively makes sense to use a physical therapy to solve a physical problem but concerns have been raised that aggressive surgery may lead to survivors in a very poor functional state. Case series report very positive experience in selected patients. One small prospective randomised controlled trial in children reported very positive outcomes. There is controversy also about how extensive the craniectomy should be, whether it should be unilateral or bilateral, and whether or not durotomy and duroplasty is performed. The Australian and New Zealand Intensive Care Society Clinical Trials Group is currently conducting a large prospective randomised multicentre study of early decompressive craniectomy for refractory intracranial hypertension (the DECRA trial) which has recruited approximately 40 patients to date.

**Drug Therapy**

There have been many unsuccessful pharmacological trials, using specific mediators and antagonists to minimize the secondary damage after TBI. In some parts of the world the buffer THAM (tromethamine, trishydroxymethyl-aminomethane) is commonly used to maintain normal pH in intracranial hypertension, though the results of the only human randomised controlled trial were equivocal. Much research focus has been on the mitigation of ‘excitotoxicity’, where abnormal levels of neurotransmitters lead to massive calcium influx and subsequent neuronal death. N-methyl-D-aspartic acid (NMDA) receptor antagonists looked promising in theory but ineffective in phase 3 trials. Other trials have examined free radical scavengers. One drug currently undergoing trials is amantadine, which acts presynaptically to enhance dopamine release and inhibit dopamine reuptake, in patients with a diffuse axonal injury. A small phase 2 trial of 35 patients suggested improved functional outcomes after 6 weeks of amantadine and this needs to further investigated in a large phase 3 study. Old drugs too are being reevaluated. Indomethacin, for example, has been postulated as a treatment for the hyperaemia subsequently seen in refractory ICH.

**Summary**

Intracranial hypertension after traumatic brain injury is a complex problem with potentially catastrophic consequences if mismanaged. Early after the injury attention must be focused on good basic intensive care with emphasis on preventing any secondary brain injury. Subsequently treatment becomes more difficult if hyperaemia develops. There are few brain specific therapies available and most human clinical trials in TBI have been disappointing. Bifrontal decompressive craniectomy is undergoing major human trials at present but needs to be properly evaluated before being generally adopted as there is the potential to save life but at the expense of numbers of severely disabled and vegetative patients.
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